



HARVARD SCHOOL OF PUBLIC HEALTH

Department of Epidemiology

Dimitrios Trichopoulos, M.D.

Vincent L. Gregory Professor of Cancer Prevention and
Professor of Epidemiology

Dr. C.W. Jameson

National Toxicology Program

Report on Carcinogens, Maryland EC-14

P.O. Box 12233

Research Triangle Park, North Carolina 27709

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RE: Saccharine delisting: A commentary by Dimitrios Trichopoulos, MD

Dear Dr. Jameson,

This response to the agency's request for comments on the National Toxicology Program's (NTP's) delisting decision on saccharin addresses the concerns of some members of the epidemiology community regarding the use and interpretation of the reviewed studies. I have been asked to review and comment on the epidemiological data by a manufacturer. The unique nature of epidemiology studies requires that the reviewer has a thorough understanding of their strengths, weaknesses, and limitations in order to accurately assess their value in supporting a finding which departs from the null hypothesis of no "association".

The vote by the National Toxicology Program Board of Scientific Counselors not to delist saccharine as a carcinogen is not supported by the opinion expressed by major scientific bodies or independent interviewers of the collective evidence (1-5). Moreover, the results of all but 2 of the investigations of a possible association between saccharine intake and

cancer of the bladder in humans were fully compatible with the null hypothesis of no association, and they were reported as such. The two exceptions are the study by Howe *et al* (6), the results of which were contradicted by those of a later investigation by his colleagues (7), and a very small case-control study by Mommsen *et al*, who found an association in women (on the basis of 6 exposed cases and 2 exposed controls) (8) but not in men (9).

The vote by the National Toxicology Program Board of Scientific Counselors may have been influenced by the Memorandum submitted on October 24, 1997 by a group of scientists (Clapp and others), and some statements made during the Carcinogens Subcommittee Meeting on October 31, 1997. Several of these statements, however, are not supported by facts, as indicated below. Page numbers refer to the minutes of the October 31, 1997 meeting, as transcribed by Kay McGovern & Associates.

- The results quoted in the Memorandum are highly selective. With over 20 relevant studies, several demographic sub-groups and several exposure levels, there are many tabular cells. The multiple comparison process is bound to generate cells with elevated odds ratios, as well as cells with reduced odds ratios. As it was pointed out by Armstrong in an earlier review (2), the cells with excess cases and the cells with excess controls are virtually balanced across studies, a phenomenon that argues in favor of randomness.
- In the Memorandum, it is stated that, Sturgeon *et al* (10), using the NCI data (11), found that heavy use of artificial sweeteners was associated with higher-grade, poorly differentiated bladder tumors. In reality, the odds ratio was 1.3 for non-invasive tumors, 1.1 for invasive tumors confined to submucosa, 1.2 for tumors invasive into musculature, and 2.3 for invasive tumors extending beyond bladder. None of these odds ratios is statistically significantly different from the null value, there is clearly no overall pattern, and the 2.3 non-significant elevation is based on only 5 exposed subjects.

- In page 23, Dr. Zahm claims that the higher mortality rates of diabetics from coronary heart disease explains why their mortality from bladder cancer is, if anything, lower than average. The low mortality of diabetics from bladder cancer has been used, as it should, as an argument that artificial sweeteners, which are consumed in high quantities by diabetics, do not cause bladder cancer (12, 13). Dr. Zahm confuses risks, that do compete, with rates that, as a rule, do not compete. Cohort studies, in general, are analyzed on the basis of rates and the rate-derived numbers of expected and observed deaths (13).
- Dr. Zahm also states (page 20) that, in the largest study (11), there was an excess of bladder cancer among high consumers of artificial sweeteners. Perhaps this expert was confused by the fact that in table 2 of the original publication (11), there is a typographical error: one-tailed P-value corresponding to $\chi^2=1.938$ is 0.08, not 0.03.
- A legitimate concern in case-control studies is that people suffering from a disease may over-report, or more completely report, exposure to a suspected factor (in this instance saccharine or artificial sweeteners in general). Dr. Zahm discounts the biasing potential of recall bias with ad hoc arguments that, although not unreasonable, completely lack empirical support (pages 44-45). It is also highly unlikely that doctors, however careless, would ever confuse a death from bladder cancer with a death from heart disease (page 24).
- Several other arguments invoked in the Meeting by those who were against the delisting of saccharine are also of questionable validity. It is stated that an effect of saccharine is more likely to be documented among persons at low risk for bladder cancer (e.g. non-smoking women), but this is true only if the effect, if any, of saccharine is additive, rather than multiplicative. The latter, though, would be more likely if an effect of saccharine were evident in heavy smoking men, as it is claimed by the same expert in the very same page of the minutes (page 20). It is also not

correct that none of the epidemiological studies have looked at *in utero* exposure to saccharine; a null study of this type was reported several years ago (14).

It is of considerable interest that suspicion of saccharine as human carcinogen was raised because there was sufficient evidence for carcinogenicity in rats. Recently, a mechanistic process explaining the rat carcinogenicity has been put forward. Nevertheless, much of the discussion in the Meeting (pp 16, 31, 73) challenges the validity of the proposed mechanism, and attempts to explain in some other way the alleged human carcinogenicity of saccharine. This is surprising, given that the vast majority of epidemiologists consider the epidemiological evidence as essentially null (5). In essence, those arguing against delisting saccharine invoke an unknown mechanism in order to explain a non-existing human evidence for carcinogenicity.

It is true that, although the epidemiological evidence is perfectly consistent with the null hypothesis of no association between saccharine intake and bladder cancer, it does not conclusively document the absence of an association. This is, however, a reflection of the logical principle that the absence of an association can never be definitely established. It is perhaps revealing, in this context, that one of the experts has stated: "I don't think I would vote to list saccharine at this point, given the epidemiology that exists, but ... I don't feel comfortable to delist it based on the epidemiology". This statement has an inherent asymmetry that challenges logic.

Sincerely,



Dimitrios Trichopoulos, MD

c.c. The Hon. Donna Shalala

References

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